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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/086,217	02/21/2002	Gregory R. Mundy	10274-063001 / A061CIP2 U	5114

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EXAMINER	
HADDAD, MAHER M	
ART UNIT	**PAPER NUMBER**
1644	

MAIL DATE	DELIVERY MODE
08/29/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/086,217	MUNDY ET AL.	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 March 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *86-98,100 and 101* is/are pending in the application.

4a) Of the above claim(s) *90* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *86-89, 91-98, 100 and 101* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

RESPONSE TO APPLICANT'S AMENDMENT

1. Applicant's amendment, filed 3/29/07, is acknowledged.

2. Claims 86-98 and 100-101 are pending.

3. Claim 90 stands withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to a nonelected invention.

4. Claims 86-89, 91-98, 100 and 101 are under consideration in the instant application as they read on a method of treating multiple myeloma with a composition comprising an anti-VLA-4 antibody and the species of chemotherapeutic agent melphalan.

5. In view of the amendment filed on 3/29/07, only the following rejection is remained.

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> *(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.*

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 86-89, 91-98, 100 and 101 stand rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Pat. No. 6,692,742 (listed previous on PTO-892) in view of Lokhorst et al (Blood 84:2269-2277, 1994) and Masellis-Smith et al (IDS Ref No. A1) for the same reasons set forth in the previous Office Action mailed 11/30/06.

Applicant's arguments, filed 3/29/07, have been fully considered, but have not been found convincing.

Applicants submit that they presented evidence showing that anti-VLA-4 antibodies and anti-IL-6 antibodies are not interchangeable for treatment of MM. Applicant concludes that one is not

permitted to make the leap that treatment of MM with anti-VLA-4 antibodies in combination with a chemotherapeutic agent is obvious in view of studies that disclose treatment of MM with anti-IL-6 receptor antibodies in combination with a chemotherapeutic agent. Applicant submits that the practitioner of ordinary skill in the art would have believed anti-α4 antibodies would not be interchangeable with anti-IL-6 receptor antibodies, or any other agent that inhibits the IL-6 pathway. Applicant refers to Dr. Gregory R. Mundy declaration , filed on 9/14/06 for support. Applicant submits that 7¶ of said declaration state that an anti-IL-6 receptor antibody with disrupt a multitude of pathways, as this receptor interacts with at least two different classes of ligands, one class being the gp130 ligands and the other class being the gp80 ligands. Applicant concludes that one would not expect that an anti-VLA-4 antibody, which disrupts very different interactions as described of the declaration that the prior art did not teach that anti-IL-6 antibodies could be used to treat MM.

It is the Examiner's position that the prior art provides for a selection of alternate molecular (IL-6 receptor or VLA-4) targets for therapeutic intervention in treating MM. Given that antibodies against alpha4 integrin inhibit cell-cell contact which is a prerequisite for IL-6 induction as taught by Lokhorst et al and because antibodies against alpha4 integrin inhibit the adhesion of alpha4beta7 integrin of B cells from MM patients with its ligand on the bone marrow (BM) fibroblast and hence prevent extravasation into the BM, it is obvious to target the upstream components of the IL-6 pathway, VLA-4, for therapeutic intervention in a method of treating MM. Inhibition of VLA-4 with antibodies blocks downstream production of IL-6 cytokine form MM cells and BMSCs, which would case proliferation and inhibits apoptosis of myeloma cells. A person of ordinary skill has good reason to pursue the known options within his or here technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense.

Further, by inhibiting the upstream VLA-4 molecule using antibodies, the skilled in the art would be targeting the same pathway of IL-6 interaction because VLA-4 is upstream of the IL-6 production.

Applicant points to Bataille et al teachings that anti-IL-6 antibodies were not effective at treating MM. Bataille et al reports that patients with advanced MM did not achieve remission or improved outcome following treatment with murine anti-IL-6 mAb antibodies.

However, the Examiner notes that both the `742 patent and the claimed invention are directed to combination therapy in treating MM. Further, the `742 claims and teach the use of anti-IL-6 receptor antibodies with melphalan to treat MM. The claims are presumed enabled. Regarding Bataille et al, the examiner notes that while the `742 patent is presumed enabled for both the advance MM as well as un-advance MM, the instant application claims do not exclude advance MM in the method of treating MM. The instant claims read on all types of MM. Further, the claims are directed to methods of treating, not methods of curing. Accordingly, any measurable level of improvement in either Bataille et al or van Zaanen et al is considered a treatment of MM.

Applicant points to 5¶ of Dr. Mundy declaration that anti-VLA-4 antibodies are believed to work through mechanisms that are independent of IL-6. Anti-VLA-4 antibodies kill myeloma cells by blocking direct interactions between myeloma cells and normal host cells in the bone marrow. When the myeloma cells cannot attach to the normal host cells, the myeloma cells die. There may be a concomitant decrease in IL-6 levels following administration of anti-VLA-4, but this would be a byproduct and not the direct cause of myeloma cell death, nor the reason why the myeloma cells dies.

Contrary to Applicant arguments Maellis-Smith *et al* show blocking adhesion of MM blood B cells to BM fibroblasts, but no cell death of MM cells with the anti-α4 antibodies. As Applicant notes that the anti-VLA-4 antibodies block direct interaction between myeloma cells and normal endothelial and fibroblast cells (host cells) which mediates MM cells extravasation into the BM and spread of the disease (see also Masellis-Smith *et al)*. Further, as Applicant notes that the downstream effect of the anti-VLA-4 antibodies is decrease in IL-6 levels which is normally augmented by the interactions between MM cells and BMSCs and leads to downstream regulatory effects of IL-6 on MM cells growth. Therefore, a person of ordinary skill has good reason to pursue the known options within his or here technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense.

Applicant points to Nakamura reference teachings that IL-6 receptor antibodies alone were ineffective in the absence of a chemotherapeutic agent for the treatment of MM. Applicant concludes that even if anti-VLA-4 antibodies inhibit IL-6, one would not expect IL-6 inhibitory agents to be interchangeable with anti-VLA-4 inhibitory agents to effectively treat MM, whether alone or in combination with any other agent.

However, the examiner notes that the scope of applicant claims encompasses the chemotherapeutic agent too. Thus the skilled in the art would still be motivated to target anti-VLA-4 antibodies in the method of treating MM to prevent MM cells extavasation into the BM, which would downregulate the production of IL-6 and regulate the MM cells growth.

Applicant contends that the Examiner is not permitted to ignore Applicant's evidence showing that VLA-4 inhibitors and IL-6 inhibitors are not interchangeable for the treatment of MM.

It is the Examiner's position that the skilled in the art would be motivated to target anti-VLA-4 antibodies in the method of treating MM to prevent MM cells extravasation into the BM, which would downregulate the production of IL-6 and regulate the MM cells growth. A person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense.

Applicant submits that three is no suggestion in any of the tree references to substitute an anti-VLA-4 antibody for an anti-IL-6 receptor antibody, and in view of the knowledge in the art regarding the different pathways by which each antibody functions, one of ordinary skill in the

art would not have a reasonable expectation of successfully treatment MM by making such a substitution.

However, the Examiner notes that KSR forecloses the argument that a specific teaching, suggestion or motivation is required to support a finding of obviousness. See the recent Board decision *Ex parte smith*,--USPQ2d--,slip op.at20,(Bd. Pat. App.&Interf. June 25, 2007) (citing KSR, 82 USPQ2d at 1396) (a available at http://www.uspto.gov/web/offices/dcom/bpai/prec/fd071925.pdf).

8. No claim is allowed.

9. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

August 20, 2007

Maher Haddad

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